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DWPI/EPAB/JPAB/USPT	(HIGH-KATHERINE-A-HERZOG-ROLAND-W	5	146
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(FILE 'HOME' ENTERED AT 15.03.18 ON 21 NOV 2000)

FILE 'MEDLINE, BIOSIS, CAPLUS' ENTERED AT 15.03.34 ON 21 NOV 2000

L1 9480 S FACTOR(W)IX
 L2 4238 S ADENO-ASSOCIATED
 L3 2567 S AAV
 L4 2406 S L3 AND (VIRUS OR VIRAL)
 L5 172970 S COAGULATION
 L6 214414 S COLLAGEN
 L7 3596 S COLLAGEN(W)IV
 L8 64931 S INTRON
 L9 1087 S (INVERTED(W)TERMINAL)(W)REPEAT?
 L10 277846 S PROMOTER?
 L11 360 S HIGH K?/AU
 L12 453 S HERZOG R?/AU
 L13 40 S (L11 OR L12) AND (L2 OR L4)
 L14 27 DUP REM L13 (13 DUPLICATES REMOVED)
 L15 105 S L1 AND (L2 OR L4)
 L16 1 S L15 AND L8
 L17 53 S L15 AND PY<1999
 L18 42 DUP REM L17 (11 DUPLICATES REMOVED)
 L19 1 S L18 AND L7
 L20 4 S L18 AND L6
 L21 853974 S MUTANT OR MUTATION?
 L22 6 S L1 AND L21 AND L7
 L23 40 S (L2 OR L4) AND INTRON?
 L24 26 DUP REM L23 (14 DUPLICATES REMOVED)
 L25 4 S L24 AND L9
 L26 27 S (L2 OR L4) AND L5 AND MUSCLE
 L27 17 DUP REM L26 (10 DUPLICATES REMOVED)
 L28 89 S L14 OR L16 OR L18 OR L19 OR L20 OR L22 OR L24 OR L27
 L29 85 DUP REM L28 (4 DUPLICATES REMOVED)
 L30 61 S L29 AND PY<1999

L30 ANSWER 2 OF 61 MEDLINE

ACCESSION NUMBER: 1998197326

MEDLINE

DOCUMENT NUMBER: 98197326

TITLE: Direct intramuscular injection with recombinant AAV vectors results in sustained expression in a dog model of hemophilia.

AUTHOR: Monahan P E, Samulski R J, Tazelaar J, Xiao X, Nichols T C,

Bellinger D A, Read M S, Walsh C E

CORPORATE SOURCE: UNC Gene Therapy Center, University of North Carolina,

Chapel Hill 27599, USA

CONTRACT NUMBER: DK09550-02 (NIDDK)

HL 48347 (NHLBI)

SOURCE: GENE THERAPY. (1998 Jan) 5 (1) 40-9.

Journal code: CCE. ISSN: 0969-7128

PUB. COUNTRY: ENGLAND: United Kingdom

Journal: Article: (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199806

AB A recombinant **adeno-associated virus (rAAV)**

vector carrying the human **factor IX** cDNA was tested for safety and therapeutic gene expression in a canine model of human hemophilia B. Intramuscular delivery of rAAV was chosen based on our previous work which described long-term (> 1.5 years) reporter gene expression in immunocompetent mice following direct **muscle** injection. For the current study, rAAV with the human **factor IX** (hF IX) cDNA under the control of the cytomegalovirus (CMV) immediate-early promoter was constructed, and rAAV/hF IX proved capable of transducing hemophilic dog primary fibroblast cultures in a dose-dependent fashion. Direct intramuscular injection of 2.5 x 10¹² rAAV/hF IX **virus** particles into the hindlimbs of a hemophilia B dog was tolerated without bleeding or systemic reaction, and the animal was asymptomatic throughout the entire study. Transient reduction in the whole blood clotting time (WBCT) occurred during the first week, with the anticipated development of an antihuman F.IX inhibitor antibody which corresponded with the loss of **coagulation** correction. At 10 weeks after vector administration, immunohistochemical analysis of injected **muscle** confirmed continued hF IX expression. Limited areas of focal lymphocytic infiltration and myofiber pathology were detected which directly correlated with positive antibody staining for helper adenovirus contamination. PCR tissue analysis revealed rAAV/hF IX DNA solely in injected **muscle** tissue and adjacent lymph node, without dissemination to other organs (including gonads). This first large animal study suggests that intramuscular gene delivery using rAAV vectors is safe and supports continued development of this approach for gene therapy of human diseases, including hemophilia B.

L30 ANSWER 3 OF 61 MEDLINE

ACCESSION NUMBER: 1998056844

MEDLINE

DOCUMENT NUMBER: 98056844

TITLE: Gene therapy for the hemophilias.

AUTHOR: Walter J. **High K A**

CORPORATE SOURCE: Department of Cardiothoracic Surgery, University of Vienna, Austria

SOURCE: ADVANCES IN VETERINARY MEDICINE. (1997) 40

119-34. Ref: 48

Journal code: CV2. ISSN: 1093-975X.

PUB. COUNTRY: United States

Journal Article: (JOURNAL ARTICLE)

General Review: (REVIEW)

(REVIEW, ACADEMIC)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199803

AB There are many lines of evidence that suggest the eventual success of gene therapy as a treatment strategy for hemophilia. Because current treatment protocols using plasma-derived or recombinant proteins are far from ideal, the safe and efficient substitution of the defective gene by a normal copy of the gene, or at least its addition, would be of great benefit to the patient and may even be a potential cure. However, the construction of efficient gene therapy vehicles has proven quite difficult in the past and, so far, there is no system that promises to have all the desired features without any serious disadvantages. In general, either the levels of transgene expression are too low (because of the low titers achieved during the generation of the **virus**) or shortened (e.g., because of the specific shut-off of the transferred promoter) as is often seen with retroviruses, or in the case of adenoviral vectors, expression is limited because of a strong immune response of the host. Clearly, much work remains to be done to optimize these promising though still imperfect vector systems. In the case of adenovirus, the development of less immunogenic vectors or in vivo modulation of the host immune system may hold promise for improvements. Reports by Yang et al. (1995) and Kay et al. (1995) are promising steps in the direction of immunomodulation. Both attenuate the immune reaction to the adenoviral vector by simultaneous application of either an interleukin or an immunoglobulin, respectively. When IL-2 was administered, the amounts of IgA were reduced and successful administration of a second dose of **virus** was possible. When CTLA4-Ig, an immunoglobulin that blocks the second signal during antigen presentation, was administered, a markedly prolonged expression of the transgene resulted. In vivo trials with **AAV** vectors have been carried out for some diseases (Flotte et al., 1993; Kaplitt et al., 1994) but not for hemophilia. Advances in high-titer **AAV** vector preparation will make this approach more feasible. The pace continues to quicken in the development of nonviral modes of gene delivery (Perales et al., 1994). Although these results are encouraging for the future of gene

therapy as a treatment for genetic diseases, much work remains to be done to make this potential alternative a reality for treatment of hemophilia.

L30 ANSWER 4 OF 61 MEDLINE

ACCESSION NUMBER: 97448273 MEDLINE

DOCUMENT NUMBER: 97448273

TITLE: Recombinant **adeno-associated** virus delivers human **factor IX** in mice [news]

AUTHOR: Stewart A

SOURCE: MOLECULAR MEDICINE TODAY. (1997 Sep) 3 (9) 368.

Journal code: CMK. ISSN: 1357-4310.

PUB. COUNTRY: ENGLAND: United Kingdom

News Announcement

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199803

L30 ANSWER 5 OF 61 MEDLINE

ACCESSION NUMBER: 97351511 MEDLINE

DOCUMENT NUMBER: 97351511

TITLE: Persistent and therapeutic concentrations of human **factor IX** in mice after hepatic gene transfer of recombinant **AAV** vectors.

AUTHOR: Snyder R O; Miao C H; Patin G A; Spratt S K; Danos O; Nagy D; Gown A M; Winther B; Meuse L; Cohen L K; Thompson A R; Kay M A

CORPORATE SOURCE: Somatix Therapy Corporation, Alameda, California 94501, USA.

CONTRACT NUMBER: HL53682 (NHLBI)

DK47754 (NIDDK)

SOURCE: NATURE GENETICS. (1997 Jul) 16 (3) 270-6.

Journal code: BRO. ISSN: 1061-4036.

PUB. COUNTRY: United States

Journal Article: (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199710

AB Haemophilia B, or **factor IX** deficiency, is a X-linked

recessive disorder that occurs in about one in 25,000 males, and severely affected people are at risk for spontaneous bleeding into numerous organs. Bleeding can be life-threatening or lead to chronic disabilities with haemophilic arthropathy. The severity of the bleeding tendency varies among patients and is related to the concentration of functional plasma **factor IX**. Patients with 5-30% of the normal **factor IX** have mild haemophilia that may not be

recognized until adulthood or after heavy trauma or surgery. Therapy for acute bleeding consists of the transfusion of clotting-factor concentrates prepared from human blood and recombinant clotting factors that are currently in clinical trials. Both recombinant retroviral and adenoviral vectors have successfully transferred **factor IX** cDNA into the livers of dogs with haemophilia B. Recombinant retroviral-mediated gene transfer results in persistent yet subtherapeutic concentrations of **factor IX** and requires the stimulation of hepatocyte replication before vector administration. Recombinant adenoviral vectors can temporarily cure the coagulation defect in the canine haemophilia B model; however, an immune response directed against **viral** gene products made by the vector results in toxicity and limited gene expression. The use of recombinant **adeno-associated virus** (rAAV) vectors is promising because the vector contains no **viral** genes and can transduce non-dividing cells. The efficacy of *in vivo* transduction of non-dividing cells has been demonstrated in a wide variety of tissues. In this report, we describe the successful transduction of the liver *in vivo* using rAAV vectors delivered as a single administration to mice and demonstrate that persistent, curative concentrations of functional human **factor IX** can be achieved using wild-type-free and adenovirus-free rAAV vectors. This demonstrates the potential of treating haemophilia B by gene therapy at the natural site of **factor IX** production.

L30 ANSWER 6 OF 61 MEDLINE

ACCESSION NUMBER: 97303212 MEDLINE

DOCUMENT NUMBER: 97303212

TITLE: Stable gene transfer and expression of human blood coagulation factor IX after intramuscular injection of recombinant adeno-associated virus.

AUTHOR: Herzog R W; Hagstrom J N; Kung S H; Tai S J;

Wilson J M; Fisher K J; High K A

CORPORATE SOURCE: Department of Pediatrics, University of Pennsylvania School of Medicine, and The Children's Hospital of Philadelphia.

Philadelphia, PA 19104, USA.

CONTRACT NUMBER: R01 HL53668 (NHLBI)

P50 HL54500 (NHLBI)

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF

THE

UNITED STATES OF AMERICA, (1997 May 27) 94 (11)

5804-9

Journal code: PV3. ISSN: 0027-8424.

PUB. COUNTRY: United States

Journal: Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199708

ENTRY WEEK: 19970803

AB We sought to determine whether intramuscular injection of a recombinant **adeno-associated virus** (rAAV) vector expressing human **factor IX** (hF.IX) could direct expression of therapeutic levels of the transgene in experimental animals. High titer (10(12)-10(13) vector genomes/ml) rAAV expressing hF.IX was prepared, purified, and injected into hindlimb **muscles** of C57BL/6 mice and Rag 1 mice. In the immunocompetent C57BL/6 mice, immunofluorescence staining of **muscle** harvested 3 months after injection demonstrated the presence of hF.IX protein, and PCR analysis of **muscle** DNA was positive for **AAV** DNA, but no hF.IX was detected in mouse plasma. Further studies showed that these mice had developed circulating antibodies to hF.IX. In follow-up experiments in Rag 1 mice, which carry a **mutation** in the recombinase activating gene-1 and thus lack functional B and T cells, similar results were seen on DNA analysis of **muscle**, but these mice also demonstrated therapeutic levels (200-350 ng/ml) of F.IX in the plasma. The time course of F.IX expression demonstrates that levels gradually increase over a period of several weeks before reaching a plateau that is stable 6 months after injection. In other experiments we demonstrate colocalization of hF.IX and **collagen IV** in intersitital spaces between **muscle** fibers. **Collagen IV** has recently been identified as a F.IX-binding protein; this finding explains the unusual pattern of immunofluorescent staining for F.IX shown in these experiments. Thus rAAV can be used to direct stable expression of therapeutic levels of F.IX after intramuscular injection and is a feasible strategy for treatment of patients with hemophilia B.

L30 ANSWER 7 OF 61 MEDLINE

ACCESSION NUMBER: 97208916 MEDLINE

DOCUMENT NUMBER: 97208916

TITLE: Recombinant adeno-associated

virus for muscle directed gene therapy.

AUTHOR: Fisher K J; Jooss K; Alston J; Yang Y; Haecker S E;

High K; Pathak R; Raper S E; Wilson J M

CORPORATE SOURCE: Institute for Human Gene Therapy, University of Pennsylvania Health System, Philadelphia 19104, USA

SOURCE: NATURE MEDICINE, (1997 Mar) 3 (3) 306-12.

Journal code: CG5. ISSN: 1078-8956.

PUB. COUNTRY: United States

Journal: Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199706
ENTRY WEEK: 19970601

AB Although gene transfer with **adeno-associated virus (AAV)** vectors has typically been low, transduction

can be enhanced in the presence of adenovirus gene products through the formation of double stranded, non-integrated **AAV** genomes. We describe the unexpected finding of high level and stable transgene expression in mice following intramuscular injection of purified recombinant **AAV** (rAAV). The rAAV genome is efficiently incorporated into nuclei of differentiated muscle fibers where it persists as head-to-tail concatamers. Fluorescent in situ hybridization of muscle tissue suggests single integration sites. Neutralizing antibody against **AAV** capsid proteins does not prevent readministration of vector. Remarkably, no humoral or cellular immune responses are elicited to the neoantigenic transgene product E. coli beta-galactosidase. The favorable biology of rAAV in muscle-directed gene therapy described in this study expands the potential of this vector for the treatment of inherited and acquired diseases.

L30 ANSWER 8 OF 61 MEDLINE
ACCESSION NUMBER: 97188484 MEDLINE
DOCUMENT NUMBER: 97188484

TITLE: Persistent expression of human clotting **factor IX** from mouse liver after intravenous injection of

adeno-associated virus vectors.

AUTHOR: Koerber D D; Alexander I E; Halbert C L; Russell D W;

Miller A D

CORPORATE SOURCE: Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA.

CONTRACT NUMBER: HL41212 (NHLBI)
DK47754 (NIDDK)
HL03100 (NHLBI)

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Feb 18) 94 (4) 1426-31.

Journal code: PV3. ISSN: 0027-8424.

PUB. COUNTRY: United States
Journal: Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199705

ENTRY WEEK: 19970505

AB We previously found that gene transduction by **adeno-associated virus (AAV)** vectors in cell culture

can be stimulated over 100-fold by treatment of the target cells with agents that affect DNA metabolism, such as irradiation or topoisomerase inhibitors. Here we show that previous gamma-irradiation increased the transduction rate in mouse liver by up to 900-fold, and the topoisomerase inhibitor etoposide increased transduction by about 20-fold. Similar rates of hepatic transduction were obtained by direct injection of the liver or by systemic delivery via tail vein injection. Hepatocytes were much more efficiently transduced than other cells after systemic delivery, and up to 3% of all hepatocytes could be transduced after one vector injection. The presence of wild-type **AAV**, which contaminates many **AAV** vector preparations, was required to observe a full response to gamma-irradiation. Injection of mice with **AAV** vectors encoding human clotting **factor IX** after gamma-irradiation resulted in synthesis of low levels of human clotting **factor IX** for the 5-month period of observation. These studies show the potential of targeted gene transduction of the liver by **AAV** vectors for treatment of various hematological or metabolic diseases.

L30 ANSWER 9 OF 61 MEDLINE
ACCESSION NUMBER: 97169874 MEDLINE
DOCUMENT NUMBER: 97169874

TITLE: Comparison of retroviral and **adeno-associated viral** vectors designed to express human clotting **factor IX**.

AUTHOR: Chen L; Perlick H; Morgan R A

CORPORATE SOURCE: Gene Transfer Technology Section, National Center for Human Genome Research, National Institutes of Health, Bethesda, MD 20892, USA.

SOURCE: HUMAN GENE THERAPY, (1997 Jan 20) 8 (2) 125-35
Journal code: A12. ISSN: 1043-0342.

PUB. COUNTRY: United States
Journal: Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199708

ENTRY WEEK: 19970801

AB Several different designs for retroviral and **adeno-associated virus (AAV)** vectors were developed to express human clotting **factor IX**. Seven separate retroviral vectors were constructed, including chimeric long terminal repeat (LTR)-based designs, vectors containing splice donor/acceptor sites with internal ribosome entry sites (IRES), and vectors with an internal cytomegalovirus (CMV)- or hepatitis B virus (HBV)-derived promoter. Five **AAV** vectors were produced using the same cassette design where a **viral** promoter was used to transcribe a

bicistronic mRNA containing **factor IX** and an IRES/neo gene. In the human hepatocyte cell line HepG2, the constructs were tested for **factor IX** production by ELISA, Northern blot, and Western blot, and for biological activity by normalization of the prolonged activated partial thromboplastin time (APTT) of **factor IX**-deficient plasma. All of the constructs produced biologically active **factor IX** in the range of 0.23-152 ng/24 hr per 10(6) cells (the HBV-promoted **factor IX AAV** vector was the least effective, and the CMV-promoted retroviral vector was the most active). Primary fibroblasts of both human and rabbit origin were also evaluated for **factor IX** production following transduction with viral vectors. Fibroblasts produced substantially more **factor IX** than the HepG2 cell line, with the best **AAV** vector synthesizing > 250 ng/24 hr per 10(6) cells and the best retroviral vector making > 900 ng/24 hr per 10(6) cells. Generally, we observed lower transduction efficiency and poorer expression with the **AAV** vectors versus retroviral vectors in these cell types.

L30 ANSWER 10 OF 61 MEDLINE
 ACCESSION NUMBER: 97008134 MEDLINE
 DOCUMENT NUMBER: 97008134
 TITLE: Identification of the endothelial cell binding site for **factor IX**
 AUTHOR: Cheung W F; van den Born J; Kuhn K; Kjellen L; Hudson B G; Stafford D W
 CORPORATE SOURCE: Department of Medical and Physiological Chemistry, University of Uppsala, Sweden.
 SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Oct 1) 93 (20) 11068-73.

JOURNAL CODE: PV3. ISSN: 0027-8424.
 PUB. COUNTRY: United States
 JOURNAL: Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; Cancer Journals
 ENTRY MONTH: 199701
 ENTRY WEEK: 19970104
 AB We previously demonstrated that the primary region of **factor IX** and IXa responsible for saturable specific binding to bovine aortic endothelial cells resides in residues 3-11 at the amino terminus of **factor IX**. We also demonstrated that **mutations** of lysine to alanine at residue 5, **factor IX** K5A, or valine to lysine at residue 10, **factor IX** V10K, resulted in a molecule unable to bind to endothelial cells. Moreover, a

mutation with lysine to arginine at residue 5, **factor IX** K5R, resulted in a **factor IX** molecule with increased affinity for the endothelial cell binding site. In this paper we report that **collagen IV** is a strong candidate for the **factor IX** binding site on endothelial cells. **Factor IX** and **factor IX** K5R compete with 125I-labeled **factor IX** for binding to tetrameric **collagen IV** immobilized on microtiter plates, while factor X, factor VII, and **factor IX** K5A or V10K fail to compete. The Kd for wild-type **factor IX** binding to **collagen IV** in the presence of heparin was 6.8 +/- 2 nM, and the Kd for **factor IX** K5R was 1.1 +/- 0.2 nM, which agrees well with our previously published Kd values of 7.4 and 2.4 nM for binding of the same proteins to endothelial cells. Our working assumption is that we have identified the endothelial cell binding site and that it is **collagen IV**. Its physiological relevance remains to be determined.

L30 ANSWER 11 OF 61 MEDLINE
 ACCESSION NUMBER: 95024009 MEDLINE
 DOCUMENT NUMBER: 95024009
 TITLE: Recombinant **adeno-associated virus** (rAAV)-mediated expression of a human gamma-globin gene in human progenitor-derived erythroid cells [published erratum appears in Proc Natl Acad Sci U S A 1995 Jan 17;92(2):646]
 AUTHOR: Miller J L; Donahue R E; Sellers S E; Samulski R J; Young N S; Nienhuis A W
 CORPORATE SOURCE: National Heart, Lung and Blood Institute, Bethesda, MD 20892.
 CONTRACT NUMBER: HL 48347-03 (NHLBI)
 SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Oct 11) 91 (21) 10183-7.

JOURNAL CODE: PV3. ISSN: 0027-8424.
 PUB. COUNTRY: United States
 JOURNAL: Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Cancer Journals; Priority Journals
 ENTRY MONTH: 199501
 AB Effective gene therapy for the severe hemoglobin (Hb) disorders, sickle-cell anemia and thalassemia, will require an efficient method to transfer, integrate, and express a globin gene in primary erythroid cells. To evaluate recombinant **adeno-associated virus** (rAAV) for this purpose, we constructed a rAAV vector encoding a human

gamma-globin gene (pJM24/vHS432A gamma). Its 4725-nucleotide genome consists of two 180-bp AAV inverted terminal repeats flanking the core elements of hypersensitive sites 2, 3, and 4 from the locus control region of the beta-globin gene cluster, linked to a mutationally marked A gamma-globin gene (A gamma) containing native promoter and RNA processing signals. CD34+ human hematopoietic cells were exposed to rAAV particles at a multiplicity of infection of 500-1000 and cultured in semisolid medium containing several cytokines. A reverse transcriptase polymerase chain reaction assay distinguished mRNA signals derived from transduced and endogenous human gamma-globin genes. Twenty to 40% of human erythroid burst-forming unit-derived colonies expressed the rAAV-transduced A gamma-globin gene at levels 4-7.1% that of the endogenous gamma-globin genes. The HbF content of pooled control colonies was 26%, whereas HbF was 40% of the total in pooled colonies derived from rAAV transduced progenitors. These data establish that rAAV containing elements from the locus control region linked to a gamma-globin gene are capable of transferring and expressing that gene in primary human hematopoietic cells resulting in a substantial increase in HbF content.

L30 ANSWER 12 OF 61 MEDLINE

ACCESSION NUMBER: 93018827 MEDLINE

DOCUMENT NUMBER: 93018827

TITLE: Definition of interferon gamma-response elements in a novel

human Fc gamma receptor gene (Fc gamma R1b) and

characterization of the gene structure.

AUTHOR: Benesh P D; Sastry K; Iyer R R; Eichbaum Q G; Raveh D P;

Ezekowitz R A

CORPORATE SOURCE: Division of Hematology/Oncology, Children's Hospital, Boston, Massachusetts

SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1992 Oct 1)

176 (4) 1115-23

Journal code: J2V. ISSN: 0022-1007.

PUB. COUNTRY: United States

Journal, Article, (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

OTHER SOURCE: GENBANK-S45704; GENBANK-S45705; GENBANK-S45707;

GENBANK-S45708; GENBANK-S45709; GENBANK-S45710;

GENBANK-S75517; GENBANK-X63232; GENBANK-X63233;

GENBANK-S40279

ENTRY MONTH: 199301

AB The human Fc gamma R1 (CD64) is a high affinity receptor for the Fc

portion of immunoglobulin (Ig), and its constitutively low expression on

the cell surface of monocyte/macrophage and neutrophils is selectively

upregulated by interferon gamma (IFN-gamma) treatment (Perussia, B., E. T.

Dayton, R. Lazarus, V. Fanning, and G. Trinchieri. 1983. J. Exp. Med.

158:1092). Three distinct cDNAs have been cloned and code for proteins that predict three extracellular Ig-like domains (Allen, J.M., and B.

Seed. 1989. Science [Wash. DC]. 243:378). Several differences in the

coding region of these cDNAs suggest that in addition to polymorphic

differences a second Fc gamma R1 gene could possibly exist. This

alternative Fc gamma R1 gene (Fc gamma R1b) was defined by the lack of a

genomic HindIII restriction site (van der Winkel, J. G. J., L. U. Ernst,

C. L. Anderson, and I. M. Chiu. 1991. J. Biol. Chem. 266:13449). We

describe the characterization a second gene (Fc gamma R1b) that has a

termination codon in the third extracellular domain and therefore predicts

a soluble form of a termination codon in the third extracellular domain

and therefore predicts a soluble form of the receptor. We also define two

distinct IFN-gamma-responsive regions in the 5' flanking sequence of Fc

gamma R1b that resemble motifs that have been defined in the class II

major histocompatibility complex promoter. The Fc gamma R1b promoter does

not possess canonical TATA or CCAAT boxes, but does possess a palindromic

motif that closely resembles the initiator sequence identified in the

terminal deoxynucleotidyl transferase/human leukocyte IFN/adenovirus

associated virus type II P5 gene promoters (Smale, S. T., and D.

Baltimore. 1989. Cell. 57:103; Seto, E., Y. Shi, and T. Shenk. 1991.

Nature [Lond.]. 354:241; Roy, A. L., M. Meisterernst, P. Pognonec, and R.

C. Roeder. 1991. Nature [Lond.]. 354:245) virus type II P5 gene promoters

raising interesting questions as to its role in the basal and

myeloid-specific transcription of this gene.

L30 ANSWER 13 OF 61 MEDLINE

ACCESSION NUMBER: 92348451 MEDLINE

DOCUMENT NUMBER: 92348451

TITLE: Chromosomal localization and organization of the murine

genes encoding the beta subunits (AIC2A and AIC2B) of the

interleukin 3, granulocyte/macrophage colony-stimulating

factor, and interleukin 5 receptors.

AUTHOR: Gorman D M; Itoh N; Jenkins N A; Gilbert D J; Copeland N G;

Miyajima A

CORPORATE SOURCE: Department of Molecular Biology, DNAX Research Institute of Molecular and Cellular Biology, Palo Alto, California

94304

CONTRACT NUMBER: NO1-CO-74101 (NCI)

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1992 Aug 5) 267

(22) 15842-8

Journal code: HIV. ISSN: 0021-9258.

PUB. COUNTRY: United States

Journal, Article, (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

OTHER SOURCE: GENBANK-M93429; GENBANK-M93722; GENBANK-M94136;
 GENBANK-M94137; GENBANK-M94138; GENBANK-M94139;
 GENBANK-M94140; GENBANK-M94141; GENBANK-M94142;
 GENBANK-M94143; GENBANK-M94144; GENBANK-M94145;
 GENBANK-M94146; GENBANK-M94147; GENBANK-M94148;
 GENBANK-M95501; GENBANK-M95502; GENBANK-M95503;
 GENBANK-M95504; GENBANK-M95505; GENBANK-M95506;
 GENBANK-M95507; GENBANK-M95508; GENBANK-M95509;
 GENBANK-M95510; GENBANK-M95511; GENBANK-M95512;
 GENBANK-M95513; +
 ENTRY MONTH: 199211

AB Chromosomal genes for two mouse homologous beta subunits (AIC2A and AIC2B)

of the interleukin-3, granulocyte/macrophage colony-stimulating factor, and interleukin-5 receptors were characterized. Both AIC2A and AIC2B genes were present on a 250-kilobase *MluI* restriction fragment and were mapped on murine chromosome 15 (these loci were provisionally designated as *Il3rb-1* (AIC2A) and *Il3rb-2* (AIC2B)), closely linked to the *c-sis* locus. Both genes consist of 14 exons and span about 28 kb each. The major transcription initiation sites of both genes were mapped at 194 bp from the initiation codon. These genes are 95% identical up to 700 bp from the transcription initiation sites. Potential recognition sequences for hemopoietic transcription factors including GATA-1 and PU 1 in addition to a TATA-like sequence are present in the 5'-flanking region. A stretch of 20 bp including the initiation site is homologous to the corresponding region of the erythropoietin receptor and the interleukin-7 receptor genes and to the initiator sequence of the **adeno-associated** virus P5 promoter, suggesting a possible role in transcription initiation. Comparison of the exon/**intron** boundaries of AIC2A and AIC2B genes with those of other members of the cytokine receptor superfamily reveals a conserved evolutionary structure. Isolation of various forms of AIC2 cDNAs reveals differential splicing of the transcripts.

L30 ANSWER 14 OF 61 MEDLINE
 ACCESSION NUMBER: 88275042 MEDLINE
 DOCUMENT NUMBER: 88275042

TITLE: Synthesis of **adeno-associated**

virus structural proteins requires both alternative mRNA splicing and alternative initiations from a single transcript

AUTHOR: Becerra S P; Kocot F; Fabisch P; Rose J A
 CORPORATE SOURCE: Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20892.

SOURCE: JOURNAL OF VIROLOGY, (1988 Aug) 62 (8) 2745-54.
 Journal code: KCV, ISSN: 0022-538X.

PUB. COUNTRY: United States

Journal: Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 198810

AB The three **adeno-associated virus** type 2

(AAV2) structural proteins (A, B, and C) are specified by transcripts generated from the most-rightward promoter (p40). Protein C (60 kilodaltons [kDa]), the most abundantly produced, is entirely contained within B (72 kDa) which, in turn, is contained within A (90 kDa). Although neither of the known structures of p40 transcripts, an unspliced 2.6-kilobase (kb) RNA and a spliced 2.3-kb RNA, possesses an AUG-initiated open reading frame that accounts for the synthesis of proteins A and B, recent evidence indicates that B is initiated by a unique eucaryotic initiation codon (ACG) (S.P. Becerra, J.A. Rose, M. Hardy, B. Baroudy, and C.W. Anderson, *Proc. Natl. Acad. Sci. USA* 82:7919-7923, 1985). In the present study, we analyzed the *in vitro* translation of **AAV** capsid proteins from synthetic transcripts and the *in vivo* expression of **AAV** mRNA constructs. The results demonstrated that **AAV** transcripts contain only one functional 5' splice donor site, that synthesis of capsid proteins from the unspliced 2.6-kb transcript is very inefficient, that transcripts without the intervening sequence (IVS) (i.e. the 2.3-kb RNA) do not produce protein A but effectively synthesize proteins B and C, and that protein A is actively synthesized from transcripts which contain the last 34 bases of the IVS. Protein A initiates within this 34-base segment in reading frame 1, apparently with the AUG codon at nucleotide 2203, and then elongates into the B and C open reading frame. Because A is inefficiently synthesized from the 2.6-kb transcript, we conclude that an effective A transcript is generated by alternative splicing and that the alternative 3' acceptor site may lie at nucleotide 2200 within a context of ...CAG[GTA]. The levels of B and C produced by a synthetic transcript devoid of the IVS suggest that the known 2.3-kb RNA is the main source of these proteins and indicate that this single RNA species expresses both proteins by alternative use of their respective initiation codons.

L30 ANSWER 15 OF 61 MEDLINE

ACCESSION NUMBER: 87321122 MEDLINE

DOCUMENT NUMBER: 87321122

TITLE: Gene expression in **adeno-associated**

virus vectors: the effects of chimeric mRNA structure, helper **virus**, and adenovirus VA1 RNA

AUTHOR: West M H; Trempe J P; Tratschin J D; Carter B J

SOURCE: VIROLOGY, (1987 Sep) 160 (1) 38-47.

Journal code: XEA, ISSN: 0042-6822.

PUB. COUNTRY: United States

Journal, Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198712

AB We used a recombinant plasmid containing an **adenovirus-associated virus (AAV)** genome to construct several vectors which express the gene for chloramphenicol acetyltransferase (CAT). We transfected four different **AAV-CAT** vectors into human 293 (adenovirus-transformed) cells and analyzed CAT activity. We show that, for vectors using the **AAV p40** and **p19** promoter, the chimeric **AAV-CAT** transcripts began from the correct 5' position but the basal level of CAT expression depended in part on the structure of the transcript. We also examined the effects of coinfection of the cells with the helper adenovirus or cotransfection with a plasmid which expressed the adenovirus translational control RNA, **VA1 RNA**. Cotransfection with plasmids containing the gene for **VA1 RNA** resulted in elevated levels of CAT activity. **VA1 RNA** stimulated translation of the chimeric mRNA. However, in two cases, the **VA1 RNA** apparently decreased the level of mRNA. These results suggest that in addition to its function in translation, **VA1 RNA** acts at a second site to alter cytoplasmic accumulation of some mRNAs. Infection with adenovirus increased CAT activity several-fold by increasing the cytoplasmic levels of the chimeric **AAV-CAT** transcript. When the CAT gene is inserted down stream of the **AAV intron**, adenovirus and not **VA1 RNA** alone increased CAT activity by promoting accumulation of a spliced transcript.

L30 ANSWER 23 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1999:100400 BIOSIS

DOCUMENT NUMBER: PREV199900100400

TITLE: Gene therapy for hemophilia.

AUTHOR(S) **High, Katherine A. (1)**

CORPORATE SOURCE: (1) Child. Hosp. Philadelphia, Abramson Res. Cent., Philadelphia, PA 19104 USA

SOURCE: Quesenberry, P. J. [Editor]; Stein, G. S. [Editor]; Forget,

B. G. [Editor]; Weissman, S. M. [Editor]. (1998) pp.

385-410. Stem cell biology and gene therapy.

Publisher: John Wiley and Sons Ltd, Baffin Lane, Chichester

PO 19 1UD, England

ISBN: 0-471-14656-0.

DOCUMENT TYPE: Book

LANGUAGE: English

L30 ANSWER 26 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1998:384830 BIOSIS

DOCUMENT NUMBER: PREV199800384830

TITLE: **AAV**-mediated gene transfer in dogs with hemophilia B.

AUTHOR(S) **Herzog, R. W. (1)**; Yang, E. Y.; Couto, L. B.; Hagstrom, J. N.; Elwell, D.; Chu, K.; Kung, S.-H.; Tai, S. J.; McQuiston, S. A.; Colosi, P.; Podsakoff, G. M.; Read, M. S.; Bellinger, D. A.; Brinkhous, K. M.; Nichols, T.; Kurtzman, G. J.; **High, K. A.**

CORPORATE SOURCE: (1) Dep. Pathol., Univ. Pennsylvania, Children's Hosp. Philadelphia, Philadelphia, PA USA

SOURCE: Journal of Investigative Medicine, (March, 1998)

Vol. 46, No. 3, pp. 215A.

Meeting Info.: Annual Meeting of the Association of

American Physicians, American Society for Clinical

Investigation, American Federation for Medical Research

1998 Biomedicine: Medical Research from Bench to Bedside

Washington, D.C., USA May 1-3, 1998 American Federation for

Medical Research

ISSN: 1081-5589.

DOCUMENT TYPE: Conference

LANGUAGE: English

L30 ANSWER 27 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1998:67366 BIOSIS

DOCUMENT NUMBER: PREV199800067366

TITLE: Absence of antibodies against **factor IX**

following IM injection of an **AAV** vector encoding a species-specific transgene.

AUTHOR(S) **Herzog, R. (1)**; Hagstrom, J.; Kung, S.; Yang, E.;

Couto, L.; Kurtzman, G.; McQuiston, S.; Colosi, P.; Elwell,

D.; Nichols, T.; Bellinger, D.; Read, M.; Brinkhous, K.;

Tai, S.; **High, K.**

CORPORATE SOURCE: (1) Child. Hosp. Phila., Philadelphia, PA USA

SOURCE: Blood, (Nov. 15, 1997) Vol. 90, No. 10 SUPPL. 1

PART 1, pp. 240A-241A

Meeting Info.: 39th Annual Meeting of the American Society

of Hematology San Diego, California, USA December 5-9, 1997

The American Society of Hematology

ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

L30 ANSWER 28 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1998 67365 BIOSIS
 DOCUMENT NUMBER: PREV199800067365
 TITLE: Sustained expression of human **factor IX** in a hemophilic canine following direct intramuscular injection of an **adeno-associated virus (AAV)** vector
 AUTHOR(S): Monahan, P. E. (1); Tazelaar, J.; Xiao, X.; Nichols, T. C.; Bellinger, D. A.; Read, M. S.; Samulski, R. J.; Walsh, C. E.
 CORPORATE SOURCE: (1) Gene Therapy Cent., Univ. N.C., Chapel Hill, NC USA
 SOURCE: Blood, (Nov. 15, 1997) Vol. 90, No. 10 SUPPL. 1
 PART 1, pp. 240A
 Meeting Info.: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997
 The American Society of Hematology
 ISSN: 0006-4971
 DOCUMENT TYPE: Conference
 LANGUAGE: English
 L30 ANSWER 29 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
 ACCESSION NUMBER: 1998 67364 BIOSIS
 DOCUMENT NUMBER: PREV199800067364
 TITLE: Persistent expression to human **coagulation factor IX** following administration of **AAV** vectors to mouse **muscle** and liver
 AUTHOR(S): Nakai, H. (1); Herzog, R.; Iwaki, Y.; Colosi, P.; Eisensmith, R.; High, K.; Kurtzman, G.; Couto, L.
 CORPORATE SOURCE: (1) Avigen Inc., Alameda, CA USA
 SOURCE: Blood, (Nov. 15, 1997) Vol. 90, No. 10 SUPPL. 1
 PART 1, pp. 240A
 Meeting Info.: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997
 The American Society of Hematology
 ISSN: 0006-4971
 DOCUMENT TYPE: Conference
 LANGUAGE: English
 L30 ANSWER 30 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
 ACCESSION NUMBER: 1998 62456 BIOSIS
 DOCUMENT NUMBER: PREV199800062456
 TITLE: Effect of anti-retroviral drugs on efficiency of transduction and expression by a recombinant **AAV** vector expressing human **factor IX**
 AUTHOR(S): Swanson, Chad M. (1); Herzog, Roland W.; Kurtzman, Gary; High, Katherine A.
 CORPORATE SOURCE: (1) Univ. Pa. Sch. Med., Children's Hosp., Philadelphia, PA

19104 USA
 SOURCE: Blood, (Nov. 15, 1997) Vol. 90, No. 10 SUPPL. 1
 PART 2, pp. 418B.
 Meeting Info.: Thirty-ninth Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997 The American Society of Hematology
 ISSN: 0006-4971
 DOCUMENT TYPE: Conference
 LANGUAGE: English
 L30 ANSWER 31 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
 ACCESSION NUMBER: 1997 523194 BIOSIS
 DOCUMENT NUMBER: PREV199799822397
 TITLE: Gene therapy for the hemophilias
 AUTHOR(S): Walter, Johannes (1); High, Katherine A.
 CORPORATE SOURCE: (1) Dep. Cardiothoracic Surgery, Univ. Vienna, Vienna Austria
 SOURCE: Dodds, W. J. [Editor]; Womack, J. E. [Editor]. Advances in Veterinary Medicine, (1997) No. 40, pp. 119-134. Advances in Veterinary Medicine: Molecular genetics, gene transfer, and therapy
 Publisher: Academic Press, Inc. 1250 Sixth Ave., San Diego, California 92101, USA
 ISSN: 0931-4229 ISBN: 0-12-039241-0
 DOCUMENT TYPE: Book, General Review
 LANGUAGE: English
 L30 ANSWER 32 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
 ACCESSION NUMBER: 1997 241624 BIOSIS
 DOCUMENT NUMBER: PREV199799540827
 TITLE: Sustained production of therapeutic levels of **factor IX** in mice following intramuscular injection of a recombinant **AAV** vector.
 AUTHOR(S): Herzog, R.; Kung, J.; Tai, S. J.; Fisher, K.; High, K. A.
 CORPORATE SOURCE: Dep. Pediatrics, Inst. Human Gene Therapy, Univ. Pennsylvania, Children's Hosp. Philadelphia, Philadelphia, PA USA
 SOURCE: Journal of Investigative Medicine, (1997) Vol. 45, No. 3, pp. 265A.
 Meeting Info.: Annual Meeting of the Association of American Physicians, the American Society for Clinical Investigation, and the American Federation for Medical Research, Biomedicine '97 Medical Research from Bench to Bedside Washington, D.C., USA April 25-27, 1997
 ISSN: 1081-5589.

DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L30 ANSWER 33 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1997:54069 BIOSIS
DOCUMENT NUMBER: PREV199799353272
TITLE: In vivo expression of therapeutic levels of human F.IX using a recombinant **adeno-associated viral (AAV)** vector.
AUTHOR(S): Kung, James (1); Hagstrom, Nathan; Walter, Johannes; Fisher, Kris; **High, Katherine A.**
CORPORATE SOURCE: (1) Univ. Pennsylvania Sch. Med., Philadelphia, PA USA
SOURCE: Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 273A.
Meeting Info.: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L30 ANSWER 34 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1997:53531 BIOSIS
DOCUMENT NUMBER: PREV199799352734
TITLE: Stable production in vitro of human coagulation **factor IX** expressed from **adeno-associated virus**.
AUTHOR(S): Wiener, S. M.; Liu, Y. J.; Shors, S.; Smith, R. H.; Chiorini, J.; Kilcoin, N.; Kotin, R. M.; Safer, B.
CORPORATE SOURCE: Molecular Hematol. Branch, Natl. Heart Lung and Blood Inst., Natl. Inst. Health, Bethesda, MD USA
SOURCE: Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 138A.
Meeting Info.: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L30 ANSWER 35 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1996:555216 BIOSIS
DOCUMENT NUMBER: PREV199699277572
TITLE: Long-term expression of human **factor IX** from mouse hepatocytes after intravenous injection of **AAV** vectors
AUTHOR(S): Koeberl, D. D. (1); Alexander, I. E.; Miller, A. D.
CORPORATE SOURCE: (1) Univ. Washington, Seattle, WA USA

SOURCE: American Journal of Human Genetics, (1996) Vol. 59, No. 4 SUPPL., pp. A46
Meeting Info.: 46th Annual Meeting of the American Society of Human Genetics San Francisco, California, USA October 29-November 2, 1996
ISSN: 0002-9297.
DOCUMENT TYPE: Conference
LANGUAGE: English

L30 ANSWER 36 OF 61 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1995:476541 BIOSIS
DOCUMENT NUMBER: PREV199598490841
TITLE: Transduction of hepatocytes in vivo with **adeno-associated virus** vectors as a model for hepatic gene therapy.
AUTHOR(S): Koeberl, D. D.; Alexander, I. E.; Miller, A. D.
CORPORATE SOURCE: Fred Hutchinson Cancer Research Center, Seattle, WA USA
SOURCE: American Journal of Human Genetics, (1995) Vol. 57, No. 4 SUPPL., pp. A43.
Meeting Info.: 45th Annual Meeting of the American Society of Human Genetics Minneapolis, Minnesota, USA October 24-28, 1995
ISSN: 0002-9297.
DOCUMENT TYPE: Conference
LANGUAGE: English

L30 ANSWER 46 OF 61 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:250667 CAPLUS
DOCUMENT NUMBER: 128:279551
TITLE: In vitro packaging of **adeno-associated virus** DNA
INVENTOR(S): Zhou, Xiaohuai; Muzyczka, Nicholas; Zolotukhin, Sergei; Ni, Tiehua
PATENT ASSIGNEE(S): Research Foundation of State University of New York, USA
SOURCE: U.S., 14 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

US 57411683 A 19980421 US 1995-477538 19950607 <--

AB A method for in vitro packaging of **adeno-associated virus** particles is described. The procedure involves the prep. of cell-free exts. contg. all the essential components for packaging. Homogeneous purified substrate DNA for packaging may be prep. sep. The in vitro packaged **AAV** particles are useful in transduction of mammalian cells and for gene therapy in animals. In one described method, the DNA packaged into **AAV** particles is not limited by the size constraints characteristic of in vivo packaged **AAV** particles.

L30 ANSWER 50 OF 61 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:752722 CAPLUS
DOCUMENT NUMBER: 128:31080

TITLE: In vitro packaging of **adeno-associated virus** DNA

INVENTOR(S): Zhou, Xiaohuai; Muzyczka, Nicholas; Zolotukhin, Sergei; Ni, Tiehua

PATENT ASSIGNEE(S): Research Foundation of State University of New York, USA

SOURCE: U.S., 14 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

US 5688676 A 19971118 US 1995-477511 19950607 <--

AB A method for in vitro packaging of **adeno-associated virus** particles is described. The procedure involves the prep. of cell-free exts. contg. all the essential components for packaging. Homogeneous purified substrate DNA for packaging may be prep. sep. The in vitro packaged **AAV** particles are useful in transduction of mammalian cells and for gene therapy in animals. In one described method, the DNA packaged into **AAV** particles is not limited by the size

constraints characteristic of in vivo packaged **AAV** particles.

L30 ANSWER 51 OF 61 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1997:686942 CAPLUS

DOCUMENT NUMBER: 127:327446

TITLE: In vitro packaging of **adeno-associated virus** DNA for therapeutic use without the formation of wild-type **virus**

INVENTOR(S): Zhou, Xiaohuai; Muzyczka, Nicholas; Zolotukhin, Sergei; Ni, Tiehua

PATENT ASSIGNEE(S): Research Foundation of State University of New York, USA

SOURCE: U.S., 15 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

US 5677158 A 19971014 US 1995-481603 19950607 <--

AB A method for in vitro packaging of **adeno-associated virus** (AAV) particles that avoids the problem of generating wild-type **virus** particles is described. The procedure involves the prep. of cell-free exts. contg. all the essential components for packaging and a post-packaging treatment to inactivate helper **virus**. The ext. includes a plasmid carrying genes for the **AAV** Rep and VP capsid proteins. Homogeneous purified substrate DNA for packaging may be prep. sep. The in vitro packaged **AAV** particles are useful in transduction of mammalian cells and for gene therapy in animals. In one described method, the DNA packaged into **AAV** particles is not limited by the size constraints characteristic of in vivo packaged **AAV** particles. In optimization expts. using a genome carrying a lacZ reporter gene, yields of 107 **AAV** particles/mL are reported.

L30 ANSWER 53 OF 61 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1997:121369 CAPLUS

DOCUMENT NUMBER: 126:127848

TITLE: In vitro packaging of **adeno-associated virus** DNA for therapeutic use without the formation of wild-type **virus**

INVENTOR(S): Zhou, Xiaohuai; Muzyczka, Nicholas; Zolotukhin, Sergei; Ni, Tiehua

Sergei Ni, Tiehua
PATENT ASSIGNEE(S) Research Foundation of State University of New York,
USA

SOURCE: PCT Int. Appl., 39 pp.

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640270	A1	19961219	WO 1996-US9263	19960605 <--
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 5686675	A	19971118	US 1995-476018	19950607 <--
CA 2222534	AA	19961219	CA 1996-2222534	19960605 <--
AU 9660947	A1	19961230	AU 1996-60947	19960605 <--
AU 706266	B2	19990610		
EP 836484	A1	19980422	EP 1996-918243	19960605 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11512923	T2	19991109	JP 1996-501621	19960605
PRIORITY APPLN. INFO.: US 1995-476018 19950607				
WO 1996-US9263 19960605				

AB A method for in vitro packaging of **adeno-assocd.** generating wild-type **virus** particles is described. The procedure involves the prep. of cell-free exts. contg. all the essential components for packaging and a post-packaging treatment to inactivate helper **virus**. The ext. includes a plasmid carrying genes for the **AAV** Rep and VP proteins. Homogeneous purified substrate DNA for packaging may be prep. sep. The in vitro packaged **AAV** particles are useful in transduction of mammalian cells and for gene therapy in animals. In one described method, the DNA packaged into **AAV** particles is not limited by the size constraints characteristic of in vivo packaged **AAV** particles. In optimization expts. using a genome carrying a lacZ reporter gene, yields of 107 **AAV** particles/mL are reported.

L30 ANSWER 54 OF 61 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996.428704 CAPLUS
DOCUMENT NUMBER: 125.78521
TITLE: Lipid vesicles containing **adeno-associated** virus rep protein for transgene integration and gene therapy

INVENTOR(S): Wiener, Stephen M.; Chiorini, John A.; Safer, Brian; Kotin, Robert M.
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
SOURCE: PCT Int. Appl., 46 pp.

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9615777	A1	19960530	WO 1995-US13190	19951116 <--
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CA 2205874	AA	19960530	CA 1995-2205874	19951116 <--
EP 786989	A1	19970806	EP 1995-943565	19951116 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10509046	T2	19980908	JP 1995-516836	19951116 <--
PRIORITY APPLN. INFO.: US 1994-344729 19941123				
WO 1995-US13190 19951116				

AB A compn. for delivering at least one DNA sequence encoding a desired portion or polypeptide (such as a therapeutic agent) to a cell is claimed.

The compn. comprises an **adeno-assocd.** virus rep protein (or a nucleic acid sequence encoding an **adeno-assocd.** virus rep protein) and a genetic construct including at least one DNA sequence encoding a protein or polypeptide or genetic transcript of interest and a promoter controlling the at least one DNA sequence. The genetic construct also includes a first **adeno-assocd.** virus ITR or portion or deriv. thereof and a second **adeno-assocd.** virus ITR or a portion or deriv. thereof. The first and second **adeno-assocd.** virus ITRs or portions or derivs. thereof flank the at least one DNA sequence encoding the protein or polypeptide or genetic transcript of interest and the promoter controlling the at least one DNA sequence encoding the protein or polypeptide or genetic transcript of interest. Such a compn. provides for integration of genetic material at a specific locus in the human chromosome, while minimizing the possibility of inadvertent inactivation of host genes and minimizing the possibility of viral contamination. Plasmid pAAVRSVF9, contg. a Rous sarcoma virus promoter fused to the human **factor IX** gene flanked by **adeno-assocd.** virus 5'- and 3'-ITR's, was constructed. Liposomes contg. this plasmid and **adeno-assocd.** virus Rep78 protein were prepd. for use in treatment of hemophilia B.

lipoprotein A1 gene under control of **viral** (vesicular stomatitis or Rous sarcoma **virus**) promoters is described

L30 ANSWER 61 OF 61 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1991:95148 CAPLUS
DOCUMENT NUMBER: 114:95148
TITLE: Polynucleotide constructs with cis-acting regulatory sequence and effector gene in therapies for infection and hyperproliferative disorders

INVENTOR(S): Goldsmith, Mark A.; Ralston, Robert O.
PATENT ASSIGNEE(S): Chiron Corp., USA
SOURCE: PCT Int. Appl., 61 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9007936	A1	19900726	WO 1990-US445	19900122 <--
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
EP 454781	A1	19911106	EP 1990-902891	19900122 <--
EP 454781	B1	19981216		
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
JP 04504843	T2	19920827	JP 1990-503423	19900122 <--
JP 2752788	B2	19980518		
EP 832980	A1	19980401	EP 1997-113730	19900122 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
JP 10179181	A2	19980707	JP 1997-320199	19900122 <--
AT 174514	E	19901115	AT 1990-902891	19900122 <--
CA 2047363	AA	19930119	CA 1991-2047363	19910718 <--
US 5861290	A	19990119	US 1992-965039	19921022 <--
US 5837510	A	19981117	US 1995-472056	19950606 <--
PRIORITY APPLN. INFO:				
US 1990-461461 19900117				
EP 1990-902891 19900122				
JP 1990-503423 19900122				
WO 1990-US445 19900122				
US 1992-965039 19921022				

AB Host cells may be treated for an infection or a hyperproliferative disorder which is characterized by the presence, in the affected cells, of a trans-acting factor capable of regulating gene expression; the therapy involves inserting into the cells a polynucleotide construct having (1) a

L30 ANSWER 58 OF 61 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:951301 CAPLUS
DOCUMENT NUMBER: 123:332111

TITLE: Integrative adenovirus expression vectors for use in gene therapy

INVENTOR(S): Deneffe, Patrice; Latta, Martine; Perricaudet, Michel; Vigne, Emmanuelle

PATENT ASSIGNEE(S): Rhone-Poulenc Rorer S.A., Fr.
SOURCE: PCT Int. Appl., 49 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9523867	A1	19950908	WO 1995-FR233	19950228 <--
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
FR 2716893	A1	19950908	FR 1994-2445	19940303 <--
FR 2716893	B1	19960412		
CA 2184113	AA	19950908	CA 1995-2184113	19950228 <--
AU 9518526	A1	19950918	AU 1995-18526	19950228 <--
EP 748385	A1	19961218	EP 1995-910605	19950228 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, NL, PT, SE				
JP 09509578	T2	19970930	JP 1995-522730	19950228 <--
ZA 9501803	A	19960109	ZA 1995-1803	19950303 <--
US 6033885	A	20000307	US 1996-702573	19960912 <--
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AB Recombination-defective adenoviruses carrying a cassette that can be integrated into the genome of host cells are constructed for use in gene therapy. The cassette particularly contains at least one inverted terminal repeat (ITR) of an **adeno-associat.**

virus (AAV) and a therapeutic gene. The use of the **AAV** ITR directs integration to the same locus in all cases and minimizes possible complications from random integration. The construction of **virus** carrying the lacZ reporter gene or a human

cis-acting regulatory sequence which is regulated by the trans-acting factor and (2) an effector gene which renders the cells susceptible to protection or destruction. The cis-acting region may be e.g. homologous to the human immunodeficiency virus (HIV) tar region, and the effector gene may encode ricin A or herpes simplex virus-1 thymidine kinase (HSV-1 tk). On infection with HIV, the HIV tat protein activates the tar region and induces prodn. of ricin A, resulting in cell death, or of HSV-1 tk, resulting in cell death with such dideoxynucleotide agents as acyclovir and gancyclovir. Thus, plasmid pTAR1, contg. the HIV long terminal repeat (including the tar sequence), a gene encoding chloramphenicol acetyltransferase (CAT), and an SV40 polyadenylation signal and t intron, was constructed. Plasmid pTAR1 was transfected into HeLa cells. Plasmid pTAT1, expressing the HIV tat trans-acting agent was transfected into half of the cells. After 48 h, cells were lysed, and lysates were incubated with ¹⁴C-labeled chloramphenicol. CAT was expressed in cells contg. both the tar-encoding plasmid and tat-encoding plasmid, but not in cells lacking the pTAT1 plasmid.